Case Report

Reactive Neutrophilic Dermatoses Associated with Nontuberculous Mycobacterial Infection in Adult-Onset Immunodeficiency Syndrome Responded Well to Acitretin: Four Cases Report

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Background: *Recent articles have suggested an adult-onset immunodeficiency syndrome that was described in HIV-uninfected adults with disseminated non-tuberculous mycobacterial infection and/or another opportunistic infection with concomitant reactive dermatoses. Few studies reported the drugs used to treat these reactive neutrophilic dermatoses including systemic steroid, etretinate, clofazimine, colchicine, and dapsone. This study aims to report the efficacy of acitretin for the treatment of this condition.*
Material and Method: *Four HIV-uninfected patients with disseminated non-tuberculous mycobacterial infection and the reactive dermatoses from department of internal medicine, Maharaj Nakorn Chiang Mai Hospital between 2008 through 2011 were observed in the clinical presentation and course of disease including treatment and response.*
Results: *All patients had at least one episode of reactive dermatoses with variable presentations comprising Sweet's syndrome with pustules, pustular vasculitis-like lesions, or generalized pustular lesions. Acitretin was prescribed to treat these reactive neutrophilic dermatoses. It showed a good response without side effects.*
Conclusion: *Acitretin, a second-generation retinoid, can be used for the treatment of reactive pustular lesions in the syndrome of adult-onset immunodeficiency due to its good response, being well tolerated, and without immunosuppression*

Keywords: *Adult-onset immunodeficiency syndrome, Non-tuberculous mycobacteria, Acitretin, Retinoid, Pustular lesions, Sweet's syndrome, Pustular vasculitis, Reactive neutrophilic dermatoses*

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Adult-onset immunodeficiency syndrome in Thai and Taiwanese patients was recently reported in HIV-uninfected adults with disseminated non-tuberculous mycobacterial infection particularly with rapidly growing mycobacteria and/or another opportunistic infection with concomitant reactive dermatoses[1]. These reactive dermatoses comprised Sweet's Syndrome, acute generalized exanthematous pustulosis (AGEP), pustular psoriasis, subcorneal pustulosis, and erythema nodosum[2-6]. A few studies reported the drugs used for the treatment of these reactive pustular lesions including systemic steroids, etretinate, clofazimine, colchicine, and dapsone[3-6].

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The present study reports four HIV-uninfected Thai patients that developed disseminated non-tuberculous mycobacterial infection with reactive pustular lesions that responded well to acitretin.

Case Reports

Case 1

A 49-year-old female who presented with lymphadenopathy in the left groin for three months with biopsy results of granulomatous lymphadenitis was started on isoniazid (I), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Two weeks later, she developed generalized tiny discrete pustules on her upper back and both thighs with multiple erythematous to violaceous plaques consisting of pustules on her hands and feet (Fig. 1). The skin biopsy report from the plaque lesion was Sweet's Syndrome. The treatment included colchicine and prednisolone

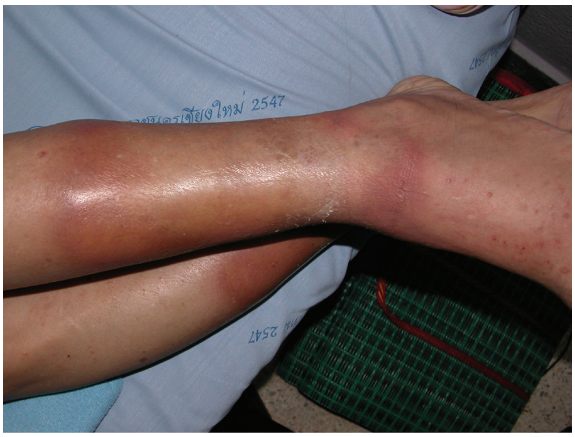

Fig. 1 Erythematous plaques on both legs showed central clearing on the left leg and many papulo-pustules on both legs and the dorsum of the left foot.

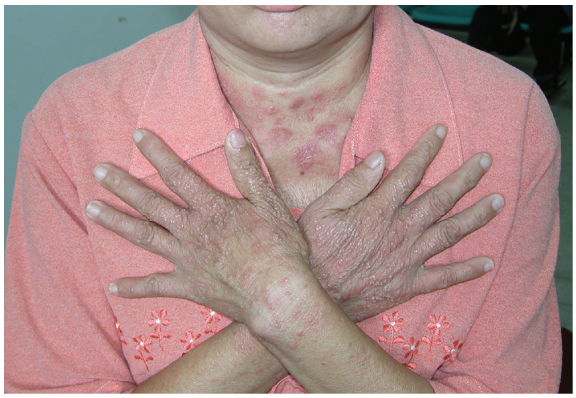

Fig. 2 Generalized multiple pustules with surrounding erythema on the upper extremities and multiple pustules on erythematous plaques on the upper chest.

40 mg/d with moderate improvement. Colchicine was changed to dapsone without further improvement. Isoniazid, rifampicin, pyrazinamide, and ethambutol were discontinued after completion then clarithromycin and moxifloxacin were prescribed because the patient's lymph nodes were not resolved. Prednisolone was tapered to 5 mg every other day. The skin lesions severely flared up with multiple generalized pustules with surrounding erythema on the upper extremities and multiple pustules on erythematous plaques on her trunk (Fig. 2). The skin biopsy was performed showing subcorneal pustules, spongioform pustules, and mixed neutrophil and lymphocyte infiltration with a rare eosinophil in the superficial dermis, which resembled pustular psoriasis and AGEP (Fig. 3). Prednisolone was increased to 15 mg/d and moxifloxacin was changed to ciprofloxacin but the skin lesions still progressed to multiple annular erythematous plaques with many pustules on the surface. Some lesions showed collarette scale, which resembled annular pustular psoriasis, on the neck, arms, shoulders, and upper back (Fig. 4). The antinuclear antibody was negative. Prednisolone was increased to 30 mg/d and acitretin 25 mg/day was added, the skin lesions dramatically improved within one week and then disappeared. Prednisolone was tapered off within four months without relapse. Then dapsone and acitretin were tapered off within nine, and twelve months respectively. One year after stopping acitretin but continuing clarithromycin and ciprofloxacin, the patient developed fever and 80-100 generalized papulo-pustules on the trunk and extremities (Fig. 5). The right axillary lymph node became enlarged and

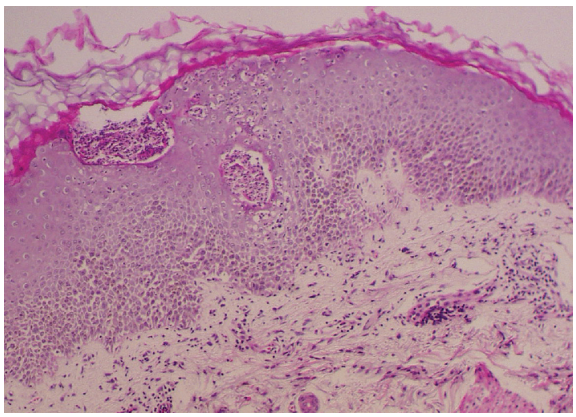

Fig. 3 Slight epidermal acanthosis, subcorneal pustules, spongioform pustules, and mixed neutrophils and lymphocytes infiltration with a rare eosinophil (H&E, x40).

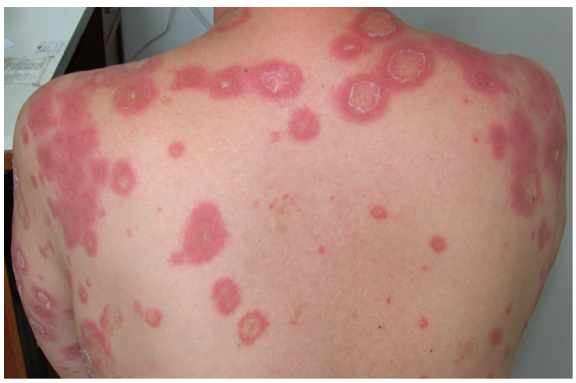

Fig. 4 Multiple annular erythematous plaques with many pustules on the surface and some lesions showed collarette scale on the neck, arms, shoulders and upper back.

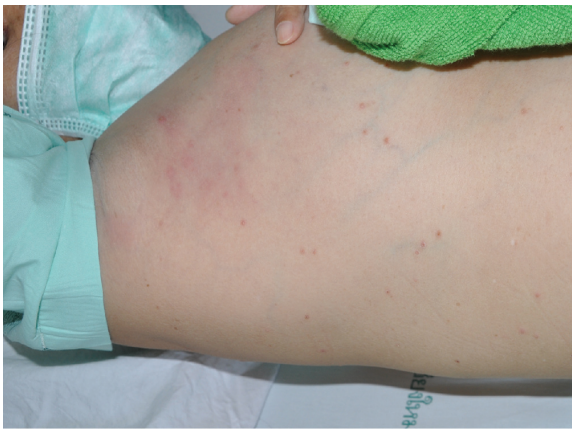

Fig. 5 Generalized multiple discrete papulo-pustules on the trunk and enlargement of right axillary lymph node.

inflamed. Acitretin 25 mg/day was again prescribed and the papulopustular lesions disappeared within ten days but the lymph node inflammation was unchanged. The lymph node culture was positive for *Mycobacterium abscessus* in this episode. The antibiotic was changed to intravenous imipenem and cilastatin sodium (Tienam®) with good results. Until now, the patient is still receiving Tienam® intravenously and acitretin 10 mg weekly. The skin lesions have not recurred and the lymph node regressed.

Case 2

A 57-year-old female presented with cervical lymphadenopathy for five months. The biopsy showed granulomatous lymphadenitis. The treatment was started with IRZE regimen that showed partial response. Two weeks after the treatment, she developed erythematous nodules on her right ear lobe, and erythematous edematous plaques with pustules on her extremities (Fig. 6). A skin biopsy from the pustules showed an intracorneal neutrophilic abscess, spongioform pustules, and diffuse perivascular and interstitial infiltration with neutrophils, eosinophils, and some lymphocytes in the superficial dermis (Fig. 7). The diagnosis was Sweet's Syndrome with pustules. Acitretin 10 mg/day was started and the skin lesions markedly improved after one week of the treatment. The acitretin was gradually tapered to 30 mg/week at the third month. Then the skin lesions with pustules recurred and the cervical lymph nodes became larger. The acitretin was increased to 10 mg/day and the skin lesions resolved. In the meantime, the lymph node culture report was positive

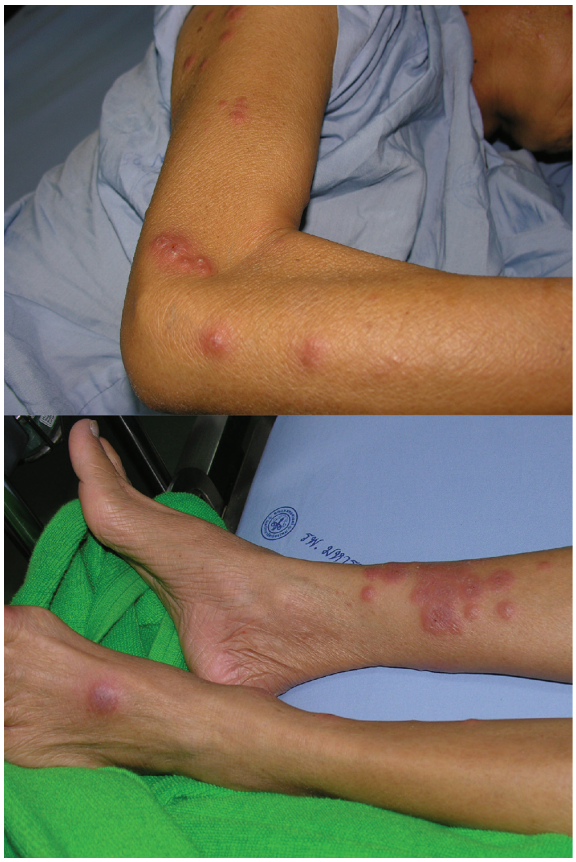

Fig. 6 Erythematous edematous plaques with pustules on the right upper limb, legs and dorsum of left foot.

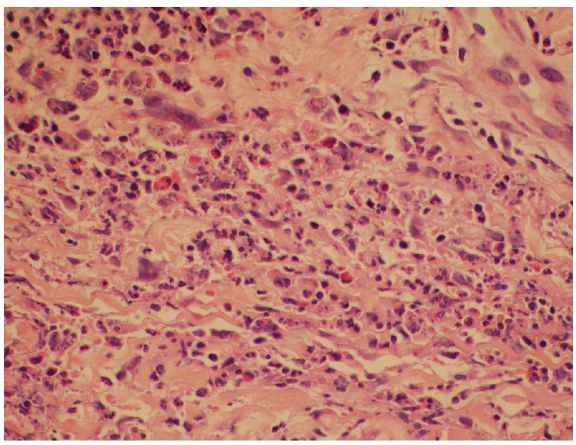

Fig. 7 Diffuse infiltrates with neutrophils and eosinophils in the superficial dermis. (H&E, x400).

for non-tuberculous mycobacteria (NTM). The treatment was changed to amikacin and cefoxitin. Two weeks later, the patient developed an acute kidney injury (AKI) from amikacin, and the antibiotics

and acitretin were stopped. Clarithromycin and ciprofloxacin were prescribed. Then the skin lesions severely flared up and transformed into generalized pustules on erythematous patches and plaques within five days (Fig. 8). After recovery from AKI, acitretin 25 mg/day was started and the antibiotics were changed to imipenem and cefoxitin. The skin lesions resolved within ten days and the enlarged lymph nodes gradually resolved (Fig. 9). One month later, the antibiotics were changed to clarithromycin and ciprofloxacin. Acitretin was gradually tapered and stopped without recurrence.

Case 3

A 59-year-old male presented with generalized multiple lymphadenopathies for five months. The biopsy from the right inguinal lymph node showed granulomatous lymphadenitis. Isoniazid, rifampicin, pyrazinamide, and ethambutol were started and his lymph nodes decreased in size initially. Two weeks after the treatment, he developed erythematous swelling plaques and superficial necrosis on hands and wrists and small edematous plaques and necrotic pustules with surrounding erythema on both feet particularly on the tips of the toes (Fig. 10, 11). The skin biopsy from the plaque lesions showed superficial dermal edema, diffused neutrophil infiltration, fragmentation of nuclei and scattered eosinophils in the upper and mid dermis. The diagnosis was pustular vasculitis-like lesions. The lymph node culture was positive for NTM. Acitretin 10 mg/day was prescribed. Clarithromycin and ciprofloxacin were prescribed. The skin lesions disappeared within one month. Acitretin was tapered and stopped in two months after the treatment without recurrence.

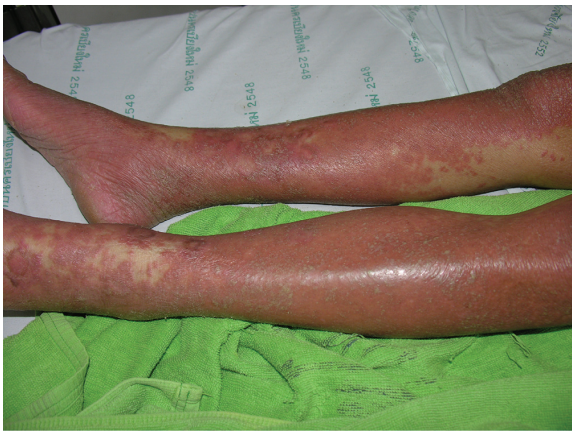

Fig. 8 Generalized pustules on erythematous patches on both lower extremities with some pustules coalescing to form lakes of pus.

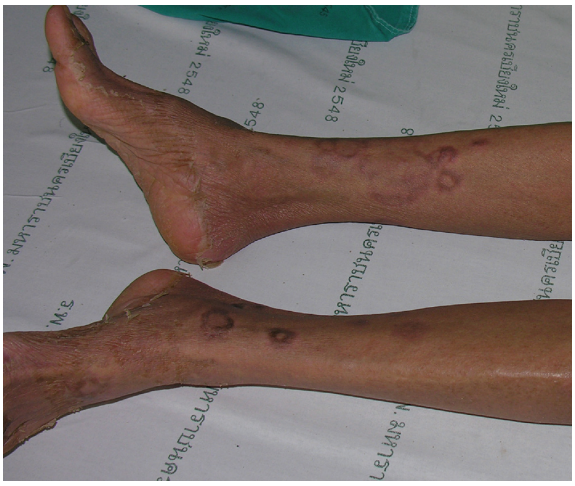

Fig. 9 Skin lesions resolved within three days after acitretin 25 mg/day was prescribed.

Case 4

A 53-year-old male presented with a skin rash for two months. Physical examination showed

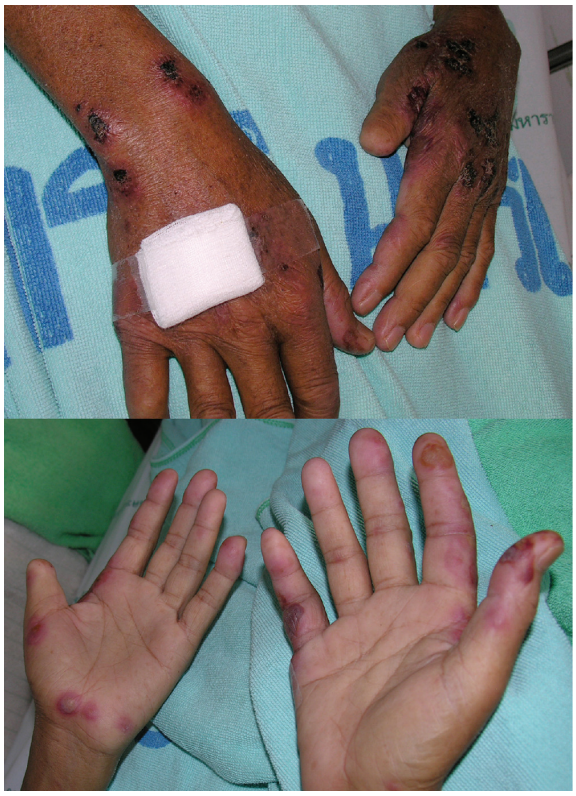

Fig. 10 Erythematous swelling plaques and superficial necrosis on hands and wrists.

edematous plaques with pustules on the face and trunk and erythematous papules and plaques with pustules and dermal hemorrhage, some areas showed superficial necrosis, on the hands and feet and generalized small lymphadenopathies (Fig. 12, 13). The lymph node culture yielded *Mycobacterium chelonae*. The skin biopsy of the right foot showed subcorneal pustule, spongioform pustule, hemorrhage in the superficial dermis, diffused neutrophils and scattered eosinophils infiltration and fragmentation of nuclei in the superficial and mid dermis, and fibrinoid deposition in some blood vessel walls. The diagnoses were Sweet's syndrome with pustules and pustular vasculitis-like lesions. Prednisolone 20 mg/d was prescribed with no response and then switched to acitretin 20 mg/day but the skin lesions did not improve. The treatment was increased to acitretin 25 mg/day. Concurrently the culture report arrived and ciprofloxacin and clarithromycin were prescribed. One week later, the pustules disappeared but the plaque lesions turned to generalized erythroderma with scale and crust and faded in two weeks.

Discussion

Adult-onset immunodeficiency syndrome is an emerging disease in East Asia particularly in Thailand[1]. The syndrome is strongly associated with high-titer neutralizing antibodies to interferon-γ[1,7]. The reactive dermatoses included Sweet's Syndrome, acute generalized exanthematous pustulosis, pustular psoriasis, subcorneal pustulosis, and erythema nodosum[2-6]. This study focused on the reactive neutrophilic dermatoses.

The patients presented with Sweet's syndrome with pustules (case 1 and case 2), pustular vasculitis-like lesions (case 3) and overlapping of both (case 4). The skin lesions in case 1 and case 2 transformed into generalized neutrophilic pustular eruptions after the antibacterial treatment. It was difficult to differentiate these lesions from drug-induced AGEP. However, the pustular eruption in case 1 flared up concurrently with the NTM lymphadenitis despite taking clarithromycin and ciprofloxacin. Therefore, it was unlikely to be AGEP from the prescribed drug. The histopathology of the pustular lesions showed subcorneal pustules and spongioform pustules that were similar to pustular psoriasis and AGEP[8]. However, the presence of eosinophils in the dermis in most of the specimens similar in AGEP suggested a hypersensitivity reaction.

Fig. 11 Small edematous plaques and necrotic pustules with surrounding erythema on the feet particularly on the tips of the toes.

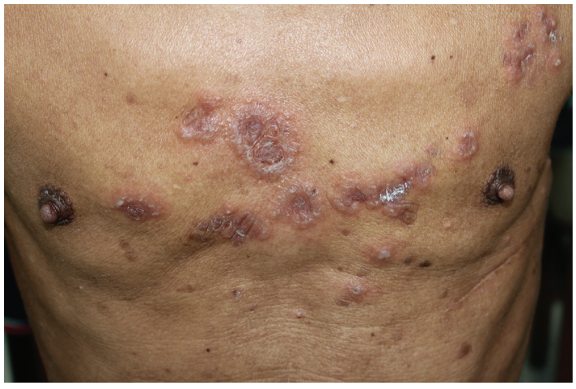

Fig. 12 Erythematous edematous plaques with pustules on the chest.

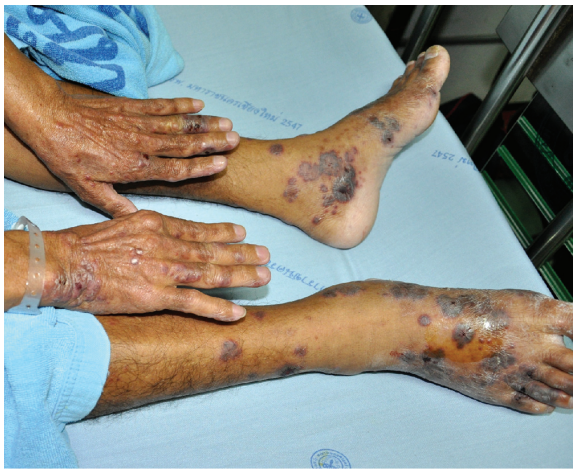

Fig. 13 Erythematous papules and plaques with pustules and dermal hemorrhage with some areas showing superficial necrosis on the hands and feet.

Table 1. Summary of the findings of the four patients

Patients	Sex, age	WBC count ($x10^9$/L)	Neutrophil (%)	NTM	Organ involvement	Duration of infection preceding pustular lesions (months)	Pus culture	Resolved after acitretin
1	F, 49	21.10	73	*M. abscessus*	Lymph node, lung, spleen	6	Negative	<1 week (1st attack) 10 days (2nd attack)
2	F, 57	20.31	79	NTM, not specified	Lymph nodes	5	Negative	1 week (1st attack) 3 weeks (2nd attack) 1 week (3rd attack)
3	M, 58	18.21	80	NTM, not specified	Lymph nodes, lung	5	Negative	<1 month
4	M, 53	34.00	75	*M. chelonae*	Lymph nodes	Simultaneously	Negative	2 weeks (+ prednisolone)

WBC = white blood cell; NTM = nontuberculous mycobacteria

The skin lesions in our patients responded very well to a low dose of acitretin. The antimicrobial treatment for NTM prevented the recurrence. There was, however, a report of neutrophilic dermatosis induced by all-trans retinoic acid[9]. There were no adverse events from acitretin in the present study. The combination with short-term oral corticosteroids was beneficial in poor responders. A higher dosage of acitretin could improve the response if corticosteroid is contraindicated. There have been many reports of acitretin in the treatment of pustular diseases including pustular psoriasis[10], subcorneal pustular dermatosis[11,12], eosinophilic pustular folliculitis[13], and AGEP[14]. The mode of action of acitretin could be from the interference of microtubular cell system and inhibition of the direct migration of the polymorphonuclear cells[15,16].

The skin lesions in our patients showed a good response to acitretin without side effects. Dosage ranged from 10 to 25 mg daily. Average time for skin lesion to resolve was about one to two weeks.

Conclusion

Acitretin, a second-generation retinoid, can be used for the treatment of these reactive pustular lesions in a syndrome of adult-onset immunodeficiency due to its good response, being well tolerated and without immunosuppressive activity.

What is already known on this topic?

Reactive neutrophilic dermatoses were found in an emerging syndrome of adult-onset immuno deficiency. The treatments using systemic steroid, etretinate, clofazimine, colchicine, and dapsone were reported.

What this study adds?

The treatment with acitretin showed a good response without significant side effects. Dosage ranged from 10 to 25 mg daily. Average time for skin lesion to resolve was about 1-2 weeks.

Potential conflicts of interest

None.

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การรักษาปฏิกิริยาผื่นผิวหนังชนิดนิวโตรฟิลเด่นที่พบร่วมกับการติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่เชื้อวัณโรคในผู้ป่วยที่เข้าได้กับภาวะกลุ่มอาการภูมิคุ้มกันบกพร่องที่เกิดในผู้ใหญ่ได้ผลดีด้วยยา acitretin: รายงานผู้ป่วย 4 ราย

สิริ เชี่ยวชาญวิทย์, มติ เชื้อมโนชาญ, พงษ์ศักดิ์ มหานุภาพ, วิไล เบาทรวง

วัตถุประสงค์: *กลุ่มอาการภูมิคุ้มกันบกพร่องที่เกิดในผู้ใหญ่ (adult-onset immunodeficiency syndrome) ประกอบด้วยผู้ป่วยผู้ใหญ่ที่ติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่เชื้อวัณโรคแบบแพร่กระจายและ/หรือติดเชื้อฉวยโอกาสอื่น ๆ และมีปฏิกิริยาตอบสนองเป็นผื่นผิวหนัง โดยผู้ป่วยกลุ่มนี้ไม่ได้ติดเชื้อเอชไอวี ยาที่มีรายงานการรักษาปฏิกิริยาของผื่นผิวหนังกลุ่มนี้ชนิดที่มีเม็ดเลือดขาวนิวโตรฟิลเด่น ได้แก่ สเตียรอยด์, etretinate, clofazimine, colchicine และ dapsone ในรายงานนี้ผู้นิพนธ์ต้องการศึกษาประสิทธิภาพของยา acitretin ในการรักษาผื่นดังกล่าว*

วัสดุและวิธีการ: *เก็บข้อมูลย้อนหลังลักษณะทางคลินิก การดำเนินโรค และการรักษา ผู้ป่วยจำนวน 4 ราย ที่ไม่ได้ติดเชื้อเอชไอวีที่มีการติดเชื้อมัยโคแบคทีเรียที่ไม่ใช่เชื้อวัณโรคแบบแพร่กระจายร่วมกับมีปฏิกิริยาตอบสนองเป็นผื่นผิวหนังชนิดที่มีเม็ดเลือดขาวนิวโตรฟิลเด่น ในภาควิชาอายุรศาสตร์ โรงพยาบาลมหาราชนครเชียงใหม่ ระหว่างปี พ.ศ. 2552-2555*

ผลการศึกษา: *ผู้ป่วยทั้ง 4 ราย มีผื่นปฏิกิริยาของผิวหนังอย่างน้อย 1 ครั้ง ระหว่างการเก็บข้อมูล โดยผื่นแสดงออกมา ในรูปแบบ Sweet's syndrome ที่มีตุ่มหนอง, ผื่นที่มีลักษณะคล้ายหลอดเลือดอักเสบชนิดมีตุ่มหนองหรือตุ่มหนองที่กระจายทั่วไป ผู้นิพนธ์ได้เลือกใช้ acitretin เพื่อรักษาผื่นดังกล่าวพบว่าได้ผลดีและไม่พบผลข้างเคียง*

สรุป: *Acitretin ซึ่งเป็นยากลุ่ม retinoid รุ่นที่ 2 สามารถนำมาใช้รักษาผื่นผิวหนังชนิดที่มีเม็ดเลือดขาวนิวโตรฟิลเด่นในผู้ป่วยที่เข้าได้กับภาวะกลุ่มอาการภูมิคุ้มกันบกพร่องที่เกิดในผู้ใหญ่ เนื่องจากมีประสิทธิภาพดี มีผลข้างเคียงน้อย และไม่กดภูมิคุ้มกัน*